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A study of the reactions involved in the preparation of luminal and related compounds

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A STUDY OF THE REACTIONS INVOLVED IN THE PREPARATION OF LUMINAL AND RELATED COMPOUNDS

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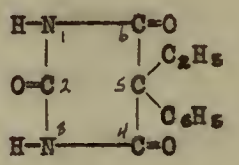
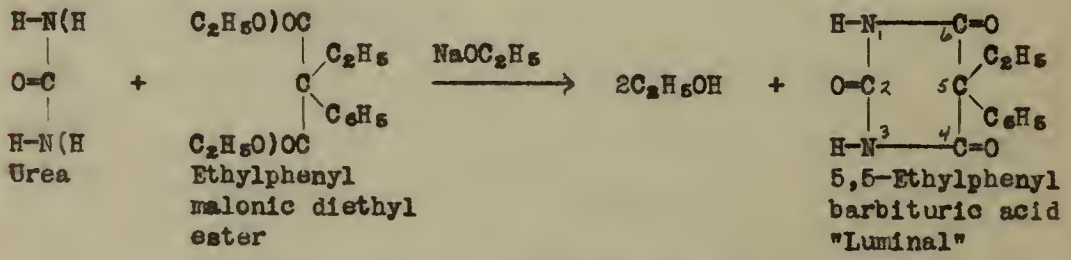
INTRODUCTION

Luminal is a substituted barbituric acid with ethyl and phenyl groups in the 5-position,



It is a member of the cyclic ureid group of hypnotic drugs, of which it is the best known and most important representative at the present time.

It is officially known as "Phenobarbital".[1] It is also, as shown by the above formula, 5,5-ethylphenyl barbituric acid and as barbituric acid is malonyl urea it may be called ethylphenyl malonyl urea. It was first prepared in 1912 by condensing ethylphenyl malonic diethyl ester with urea.[2]



It was introduced under the name of "Luminal" by "Die Farbenfabricken vorm. Friedr. Bayer & Co., Elberfeld, Germany". H. Hoerlein took out patents[3] for them in this country in 1912 with the same names and same methods of preparation.

The action of "Luminal" is that of a hypnotic and sedative when introduced into the body subcutaneously or internally.[4]

The uses are numerous as it has been found to be useful in the following types of cases: insomnia and conditions of excitement

of the nervous system, wakefulness of mania, delirium, dementia praecox, hysteria, maniac depressive insanity, epilepsy, arteriosclerosis, morphine withdrawal, and post-apoplectic conditions.[4]

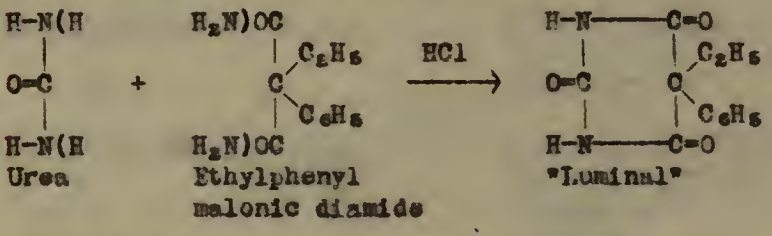
The doses are from 0.03-0.3 Gram (1/2-5 grains), increased, if necessary; average dose 0.03 Gram (1/2 grain)—maximun dose: 0.8 Gram (12 grains)—the dose should be much weaker for women, weak men, and phthisical subjects.[4]

Since "Luminal" has proven to be one of the group of valuable synthetic remedies whose manufacture is a matter of importance, the three following objectives were attempted in the present investigation: (1) To make any improvements in the known methods of preparation; (2) To prepare a number of substituted barbituric acids with alkyl and aryl groups in the 5-position; and (3) To introduce the phenyl radical into the malonic ester by direct means.

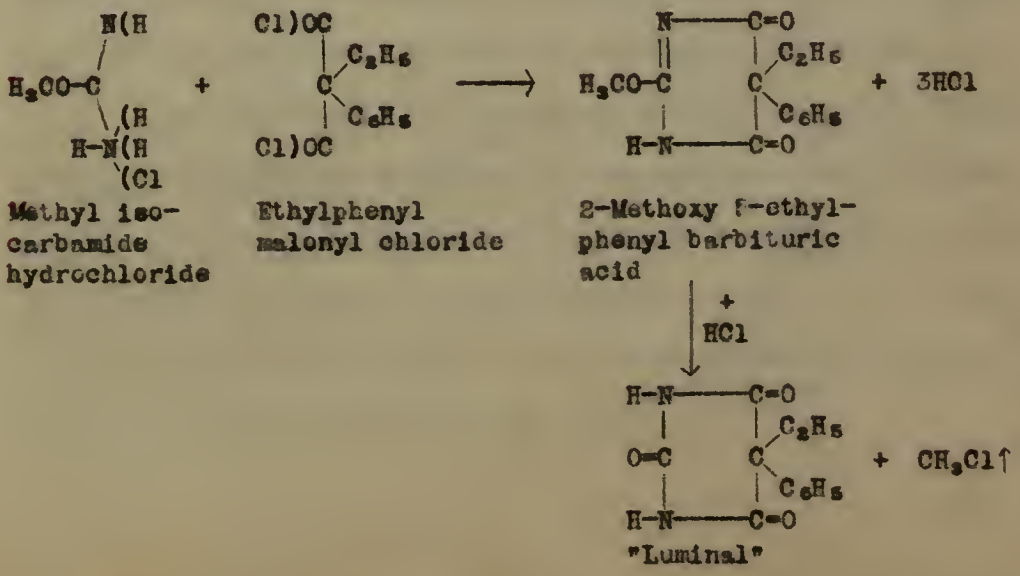
THEORETICAL DISCUSSION AND REVIEW OF LITERATURE

In as much as the investigation began with a known method of preparation of "Luminal", the different syntheses of it will be taken up in the chronological order in which they appeared.

According to the patent specifications[6] of "Die Farbenfabricken vorm. Friedr. Bayer & Co., Elberfeld, Germany", "Luminal" could be prepared by the following methods: (1) By condensing urea with ethylphenyl malonic diethyl ester according to the reaction as just given (page 1).(2) By condensing ethylphenyl malonic diamide with urea according to the following reaction:



(3) From ethylphenyl malonyl chloride and methyl isocarbamide. This reaction yields first, 2-methoxy 5,5-ethylphenyl barbituric acid, and this, when warmed with 30% hydrochloric acid, evolves methyl chloride and yields "Luminal". The reactions may be represented as follows:



As a consequence of the World War the German patents were cancelled in this country. The preparation of "Luminal" was undertaken in 1918 as a war measure by M. Rising and J. Stieglitz.[6] The procedure followed at that time is summarized in the following series of reactions:

$$C_6H_5CH_2CN + CH_3OH + HCl + H_2O \longrightarrow C_6H_5CH_2CO_2CH_3 + NH_4Cl$$

Benzyl cyanide — Phenylacetic methyl ester

$$C_6H_5CH_2CO_2CH_3 + (CO_2CH_3)_2 \xrightarrow{CH_3ONa} CH_3O_2CC(ONa)=C(C_6H_5)(CO_2CH_3) + 2CH_3OH$$

Phenylacetic methyl ester — Dimethyl oxalate — Sodium oxalylphenylacetic dimethyl ester

$$CH_3O_2CC(ONa)=C(C_6H_5)(CO_2CH_3) \xrightarrow{H_2SO_4} CH_3O_2CCOCH(C_6H_5)(CO_2CH_3) + NaHSO_4$$

Oxalylphenylacetic dimethylester

$$CH_3O_2CCOCH(C_6H_5)(CO_2CH_3) \xrightarrow{90^\circ C.} C_6H_5CH(CO_2CH_3)_2 + CO\uparrow$$

Phenylmalonic dimethylester

$$C_6H_5CH(CO_2CH_3)_2 + C_2H_5I \xrightarrow{NaOCH_3} (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NaI + CH_3OH$$

Ethylphenylmalonic dimethylester

$$(C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + CO(NH_2)_2 \xrightarrow{NaOCH_3} (C_6H_5)(C_2H_5)C(CONHCONH)CO + 2CH_3OH$$

Urea — "Luminal"

From the above reactions it is obvious that the ethyl ester may be substituted throughout for the methyl ester. With these views in mind the possible synthesis of "Luminal" by means of the ethyl ester was studied. The method of preparation of the phenylmalonic ester was in both cases according to the method of Wislicenus.[7]

The desirability of obtaining ethylphenyl malonic dimethyl ester, an intermediate necessary in their synthesis for "Luminal", in better yield led M. Rising and Tsoh-Hu Zee[8] to the study of a number of other methods for its preparation. Of these, the one expressed in the reactions which follow has proved successful in obtaining the product, but not in increasing the yield.

$$C_6H_5CH_2CN + NH_2Na + C_2H_5I \longrightarrow C_6H_5CH(C_2H_5)(CN) + NaI + NH_3\uparrow$$
Benzyl cyanide — Phenylbutyronitrile

$$2C_6H_5CH(C_2H_5)(CN) + 2Na \longrightarrow 2C_6H_5CNa(C_2H_5)(CN) + H_2\uparrow$$
Sodium salt of phenylbutyronitrile

$$C_6H_5CNa(C_2H_5)(CN) + ClCO_2CH_3 \longrightarrow NaCl + C_6H_5C(CO_2CH_3)(C_2H_5)(CN)$$
Chloroformic methylester — Ethylphenylcyanoacetic methylester

$$C_6H_5C(CO_2CH_3)(C_2H_5)(CN) + H_2O + CH_3OH \xrightarrow{HCl} (C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + NH_4Cl$$
Ethylphenylmalonic dimethylester

$$(C_6H_5)(C_2H_5)C(CO_2CH_3)_2 + CO(NH_2)_2 \xrightarrow{NaOCH_3} (C_6H_5)(C_2H_5)\overline{C(CONHCONH)CO} + 2CH_3OH$$
Urea — "Luminal"

Another method of synthesis of ethylphenylmalonic dimethyl ester was reported later by M. Rising and Tsoh-Wu Zee[9] in which the total yield of the ester calculated from the amount of phenylacetonitrile used, was 43.1%, as compared with 27.4% by the first method of Zee above and 41% in the war-time synthesis. The later plan makes use of the following reactions:

$$C_6H_5CH_2CN + NaNH_2 + C_2H_5I \longrightarrow (C_6H_5)(C_2H_5)CH(CN) + NaI + NH_3\uparrow$$
Benzyl cyanide — Phenylbutyronitrile

$$(C_6H_5)(C_2H_5)CH(CN) + CH_3OH + H_2O \xrightarrow{HCl} (C_6H_5)(C_2H_5)CH(CO_2CH_3) + NH_4Cl$$
Ethylphenylacetic methylester

$$2(C_6H_5)(C_2H_5)CH(CO_2CH_3) + 2Na \longrightarrow H_2\uparrow + 2(C_6H_5)(C_2H_5)CNa(CO_2CH_3)$$
Sodium salt of ethylphenylacetic methylester

$$(C_6H_5)(C_2H_5)CNa(CO_2CH_3) + ClCO_2CH_3 \longrightarrow NaCl + (C_6H_5)(C_2H_5)C(CO_2CH_3)_2$$
Chloroformic methylester — Ethylphenylmalonic dimethylester

For the synthesis of "Luminal" further methods of preparation of the intermediate phenyl malonic diethyl ester have been recently described by Nelson and Cretcher.[10] In as much as it was their purpose to prepare a number of derivatives of phenyl barbituric acid, it appeared to them highly desirable to have a method

as satisfactory as possible for the preparation of phenylmalonic diethylester, an intermediate useful for the preparation of all of them including of course "Luminal". For this reason considerable time was devoted by them to a study of the synthesis of this compound, that is, phenylmalonic diethylester.

They first attempted to prepare phenylmalonic diethylester by the condensation of phenylacetic ethylester with diethyl carbonate. The reaction is as follows:

$$\underset{\text{Phenylacetic ethylester}}{C_6H_5CH_2CO_2C_2H_5} + \underset{\text{Diethyl carbonate}}{CO_3(C_2H_5)_2} \longrightarrow \underset{\text{Phenylmalonic diethylester}}{C_6H_5CH(CO_2C_2H_5)_2} + C_2H_5OH$$

Their yield of 20% was in accord with the observations of Volhard[11] and of Scheibler and Mahboub.[12]

Their attention was then directed to phenylacetonitrile as a suitable intermediate for their purpose. The sodium salt of phenylacetonitrile was condensed with chloroformic ethylester to give a yield of 50%. The method followed was that of Rising and Tsoh-Wu Zee.[8] The reaction may be represented as follows:

$$\underset{\substack{\text{Sodium salt of}\\ \text{phenylaceto-}\\ \text{nitrile}}}{C_6H_5CH(Na)(CN)} + \underset{\substack{\text{Chloro-}\\ \text{formic}\\ \text{ethylester}}}{ClCO_2C_2H_5} \longrightarrow NaCl + \underset{\substack{\text{Phenylcyanoacetic}\\ \text{ethylester}}}{C_6H_5CH(CN)(CO_2C_2H_5)}$$

They next studied the condensation of phenylacetonitrile with diethyl carbonate according to the method of Hessler.[13] The reaction may be represented as follows:

$$\underset{\substack{\text{Phenylaceto}\\ \text{nitrile}}}{2C_6H_5CH_2CN} + \underset{\substack{\text{Diethyl}\\ \text{carbonate}}}{2(C_2H_5)_2CO_3} + 2Na \longrightarrow H_2\uparrow + 2C_2H_5OH + \underset{\substack{\text{Phenylcyano-}\\ \text{acetic ethylester}}}{2C_6H_5CH(CN)(CO_2C_2H_5)}$$

The method of Hessler for preparing phenylcyanoacetic ethylester was also studied in the present investigation because of its ease of preparation in the laboratory and the ease with which it is converted to phenylmalonic diethylester.

Nelson and Cretcher continued their study of the condensation of phenylacetonitrile with ethyl carbonate according to the method of Bodroux.[14]

$$\underset{\text{Phenylaceto nitrile}}{C_6H_5CH_2CN} + \underset{\text{Diethyl carbonate}}{(C_2H_5)_2CO_3} \xrightarrow{NaNH_2} \underset{\text{Phenylcyanoacetic ethylester}}{C_6H_5CH(CN)(CO_2C_2H_5)} + C_2H_5OH + NH_3\uparrow$$

Since phenylmalonic esters are not alkylated in good yield, they thought it might be an advantage to alkylate phenylacetonitrile before attempting to introduce the second carboxyl group. In no case, however, did they succeed in condensing a substituted phenylacetonitrile with ethylcarbonate. The reactions may be expressed as follows:

$$\underset{\text{Phenyl-acetonitrile}}{C_6H_5CH_2CN} + NaNH_2 + C_2H_5I \longrightarrow \underset{\text{Phenylbutyronitrile}}{(C_6H_5)(C_2H_5)CH(CN)} + NH_3 + NaI$$

$$\text{but } (C_6H_5)(C_2H_5)CH(CN) + \underset{\text{Diethyl carbonate}}{(C_2H_5)_2CO_3} \longrightarrow \text{Nil}$$

They converted phenylcyanoacetic ethylester to phenylmalonic diethylester by the method of Wislicenus[15] and such was the method adopted in the present investigation. The reaction may be expressed as follows:

$$\underset{\text{Phenylcyanoacetic ethylester}}{C_6H_5CH(CN)(CO_2C_2H_5)} + HOH + C_2H_5OH \xrightarrow{HCl} NH_4Cl + \underset{\text{Phenylmalonic diethylester}}{C_6H_5CH(CO_2C_2H_5)_2}$$

The ethylation of phenylmalonic diethylester according to Wislicenus[16] is shown by the following reaction:

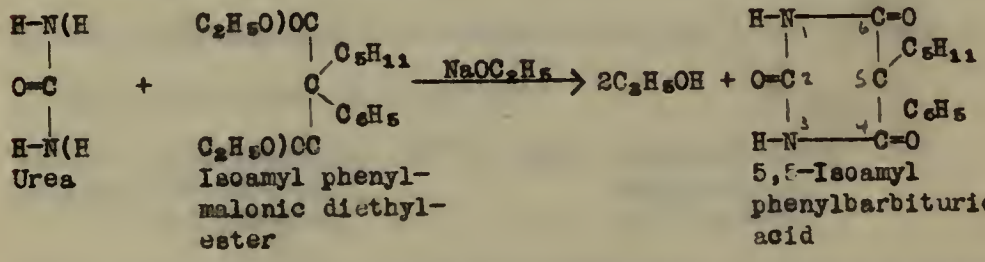
$$\underset{\text{Phenylmalonic diethylester}}{C_6H_5CH(CO_2C_2H_5)_2} + C_2H_5I \xrightarrow{NaOC_2H_5} \underset{\text{Ethylphenylmalonic diethylester}}{(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2} + NaI + C_2H_5OH$$

This method is general for the alkylation of the malonic esters and was used in the present investigation with a modification.

The phenyl substituted methylene group ($C_6H_5\overset{|}{C}-H$) between the two carbonyl groups (CO) in the phenylmalonic ester is highly reactive and the hydrogen may be readily replaced by an alkyl group. For that reason an attempt was made to condense phenyl malonic diethylester with iso-amyl iodide to prepare iso-amyl phenylmalonic diethylester according to the following reaction:

$$\underset{\text{Phenylmalonic diethylester}}{C_6H_5CH(CO_2C_2H_5)_2} + \underset{\text{Isoamyl iodide}}{(CH_3)_2CHCH_2CH_2I} \xrightarrow{NaOC_2H_5} C_2H_5OH + \underset{\text{Isoamyl phenylmalonic diethylester}}{(C_6H_5)(C_5H_{11})C(CO_2C_2H_5)_2} + NaI$$

Then it appeared highly desirable to condense isoamyl phenylmalonic diethylester with urea to form 5,5-isoamylphenyl barbituric acid according to the following:



Thus by proper selection of an alkyl halide, a large number of substituted phenylbarbituric acids may be synthesized.

Isoamyl phenylmalonic diethylester and 5,5-isoamyl phenylbarbituric acid would be two new contributions to the field of organic chemistry and the latter may be of value as a hypnotic and sedative because of its similar structure to "Luminal".

Of interest is the preparation of phenylmalonic ethylester mono-amide and diamide by treating phenylmalonic diethylester with alcoholic ammonia according to the method of Wislicenus.[17] The reactions may be expressed as follows:

$$\underset{\text{Phenylmalonic diethylester}}{C_6H_5CH(CO_2C_2H_5)_2} + NH_3 \xrightarrow{C_2H_5OH} C_2H_5OH + \underset{\text{Phenylmalonic ethylester mono-amide}}{C_6H_5CH(CONH_2)(CO_2C_2H_5)}$$

$$\text{and } C_6H_5CH(CO_2C_2H_5)_2 + 2NH_3 \xrightarrow{C_2H_5OH} 2C_2H_5OH + \underset{\text{Phenylmalonic diamide}}{C_6H_5CH(CONH_2)_2}$$

The condensation of diamide with urea is another general method of preparing barbituric acid derivatives according to the reaction given on page 3.

All the methods for preparing the important intermediate, i.e., the dimethyl or diethyl esters of phenyl malonic acid have been by indirect means. That is, one starts with benzyl cyanide and builds up this compound, to prepare phenylmalonic diethylester. Therefore the attempt was made in this investigation to obtain phenylmalonic diethylester by the direct introduction of the phenyl radical into the malonic ester or into the ethylmalonic ester.

It was first attempted to prepare phenylmalonic diethylester by the condensation of bromomalonic diethylester and benzene by means of the "Friedel-Crafts' Reaction":

$$\underset{\text{Benzene}}{C_6H_5(H} + \underset{\substack{\text{Bromomalonic}\\ \text{diethylester}}}{Br)HC(CO_2C_2H_5)_2} \xrightarrow{AlCl_3} HBr\uparrow + \underset{\substack{\text{Phenylmalonic}\\ \text{diethylester}}}{C_6H_5CH(COC_2H_5)_2}$$

The directness of the method is the important advantage which this procedure would have over that in common use.

The investigation was then directed to condensation of phenetole and malonic diethylester according to the following reaction:

$$\underset{\text{Phenetole}}{C_6H_5OC_2H_5} + \underset{\substack{\text{Malonic}\\ \text{diethylester}}}{H_2C(CO_2C_2H_5)_2} \longrightarrow H_2O + \underset{\substack{\text{Ethylphenylmalonic}\\ \text{diethylester}}}{(C_6H_5(C_2H_5)C(CO_2C_2H_5)_2}$$

The condensation of bromomalonic diethylester and benzene was again studied with zinc dust as a condensing agent. The expected reaction was as follows:

$$\underset{\text{Benzene}}{2C_6H_5H} + \underset{\substack{\text{Bromomalonic}\\ \text{diethylester}}}{(Br)HC(CO_2C_2H_5)_2} + Zn \longrightarrow ZnBr_2 + H_2\uparrow + \underset{\substack{\text{Phenylmalonic}\\ \text{diethylester}}}{C_6H_5CH(CO_2C_2H_5)_2}$$

No attempts were made to prepare the important intermediate, phenylmalonic diethylester, by the following methods: (1) By trying to

hydrolyze phenylmalonic dinitrile in the presence of ethyl alcohol. In this case the reaction took other than the desired course.[16] (2) The hydrolysis of phenylcyanoacetic acid, which yields products other than expected.[16] (3) The introduction of the phenyl radical into the malonic ester by means of brombenzene and sodium alcoholate. This however as stated by Wislicenus[7] is wrecked on account of the stability of the halogen benzene.

EXPERIMENTAL PART

The experimental work of this investigation was divided into the following separate studies:

I. The Preparation of "Luminal" according to M. Rising and J. Stieglitz,

II. The Preparation of "Luminal" by means of the Ethyl Ester according to the method of Rising and Stieglitz,

III. The Preparation of "Luminal" according to W. Nelson and L. Gretcher,

IV. The Preparation of the Amides of Phenyl Malonic Acid,

V. The Preparation of 5,5-Isoamyl Phenyl Barbituric Acid,

VI. The Condensation of Bromomalonic Diethyl Ester and Benzene,

VII. The Condensation of Malonic Diethyl Ester and Phenetole, and

VIII. The Condensation of Ethyl Bromomalonic Diethyl Ester and Iodobenzene.

I. The Preparation of "Luminal" according to M. Rising and J. Stieglitz[6]

This method is indicated in the series of reactions as given previously on page 4.

(1) Dimethyl oxalate is condensed with the methyl ester of phenylacetic acid in absolute ether solution by means of sodium wire and a few drops of methyl alcohol.

Wislicenus,[7] who first carried out this reaction with the ethyl ester, recommended, as the condensing, agent the use of pure

sodium ethylate, which is prepared by driving off the excess alcohol in a stream of inert gas (hydrogen) from a solution of sodium ethylate in alcohol.

In this stage of the synthesis Rising and Stieglitz found it desirable to prepare the sodium salt of the dimethyl ester of oxalyl phenyl acetic acid according to an earlier method of Wislicenus,[19] that is, effecting the condensation by the use of sodium wire which is activated by the presence of a few drops of absolute methyl alcohol. The use of methyl alcohol to activate the reaction is the modification used by Rising and Stieghtz and gives 85% to 92% yield as compared to an 85% yield obtained by Wislicenus using alcohol-free sodium ethylate.

$$(COOCH_3)_2 + C_6H_5CH_2CO_2CH_3 \xrightarrow{NaOCH_3} CH_3O_2CC(ONa)=C(C_6H_5)(CO_2CH_3) + 2CH_3OH$$

Dimethyl oxalate — Phenylacetic methyl ester — Sodium oxalylphenylacetic dimethyl ester

(2) In the next stage of the synthesis, the dimethyl ester of oxalyl phenyl acetic acid is converted into the dimethyl ester of phenyl malonic acid by heat and the loss of CO, according to the method used by Wislicenus on the ethyl ester.[7]

$$CH_3O_2CCOCH(C_6H_5)CO_2CH_3 \longrightarrow CO\uparrow + C_6H_5CH(CO_2CH_3)_2$$

Oxalylphenylacetic dimethylester — Phenylmalonic dimethylester

Rising and Stieglitz claimed that in the use of the methyl ester the phenyl malonic dimethyl ester is a solid which may be easily purified by recrystallization, whereas the ethyl ester as obtained by this method is a liquid, which tends to decompose when distilled, even in vacuo.

(3) The ethylation of phenyl malonic dimethyl ester in alcoholic solution according to the directions of Rising and Stieglitz leads to not altogether satisfactory yields as observed in this

investigation. In fact no product could be obtained that would crystallize at room temperature, as claimed by Rising and Stieglitz, until a modification was made in the procedure. It was found in this investigation that saponification and decomposition of the desired ester could be prevented by using absolute ether for the solvent in which the refluxing may take place at a lower temperature. The use of absolute ether also permits one to view the course of the reaction.

The yield of crude ethyl phenyl malonic diethyl ester was 84% as compared with 75% obtained by Rising and Stieglitz which could not be duplicated in this investigation with the conditions under which they carried out the ethylation.

$$\underset{\text{Phenylmalonic dimethylester}}{C_6H_5CH(CO_2CH_3)_2} + C_2H_5I \xrightarrow{NaOCH_3} \underset{\text{Ethylphenylmalonic dimethylester}}{(C_6H_5)(C_2H_5)C(CO_2CH_3)_2} + CH_3OH + NaI$$

(4) The condensation of ethyl phenyl malonic dimethyl ester with urea is the last stage in the synthesis of "Luminal".

$$\underset{\text{Ethylphenylmalonic dimethylester}}{(C_6H_5)(C_2H_5)C(CO_2CH_3)_2} + \underset{\text{Urea}}{CO(NH_2)_2} \xrightarrow{NaOCH_3} \underset{\text{"Luminal"}}{(C_6H_5)(C_2H_5)\overline{CCONHCONH}CO}$$

According to patent specifications[8] the condensation is effected by sodium alcoholate in alcoholic solution by heating the mixture under a reflux condenser. Rising and Stieglitz found that this produced "Luminal" in exceedingly small quantity, (10%). They claimed that a far better result (40% yield) was obtained with the method of Fischer[20] which makes use of the sealed tube. The use of sodium methylate in alcoholic solution instead of sodium ethylate is the only modification of Fischer's method by Rising and Stieglitz.

The investigation revealed the following: (1) That it made no difference in the yield or product whether sodium methylate or

sodium ethylate was used; (2) That there was no need of removing the unchanged ester, as directed, with ligroin, since the "Luminal" is easily extracted from the crude product with boiling water; and (3) That a pressure flask may be substituted for the sealed tube with the same advantage as obtained with the latter.

Procedure

(1) Benzyl Cyanide, $C_6H_5CH_2CN$, was prepared four times according to the directions of Roger Adams[21]

$$C_6H_5CH_2Cl + NaCN \longrightarrow NaCl + C_6H_5CH_2CN$$

Benzyl chloride — Benzyl cyanide

The materials taken were as follows:

Benzyl chloride (practical).....1000 g.

Sodium cyanide (96% to 98%).....500 g.

Water.....450 g.

Ethyl alcohol (95%).....1000 g.

In a 5-liter round-bottom flask, fitted with a stopper holding a reflux condenser and a separatory funnel, were placed 500 g. of powdered sodium cyanide and 450 c.c. of distilled water. The mixture was warmed on a hot water bath to dissolve most of the sodium cyanide, and then 1000 g. of benzyl chloride were mixed with 1000 g. of 95% ethyl alcohol and run in through the separatory funnel during the course of one-half to three-quarters of an hour. The mixture was then heated in a hot water bath (temperature between 82 to 86° C) for four hours. In later experiments it was warmed for a longer period, that is, six to eight hours, as it was noticed that the formation of more sodium chloride later on indicated that the reaction was not complete at the end of four hours. The mixture

was then cooled and filtered with suction to remove most of the sodium chloride. The precipitate was washed with small portions of ethyl alcohol to remove any benzyl cyanide which may be mechanically held. The flask was fitted with a condenser and as much ethyl alcohol as possible was distilled off on a steam bath. Later experiences showed that more ethyl alcohol and water is removed when heated in a brine bath, i.e., a saturated solution of rock salt which gives a temperature of 105 to 108°C. The residual liquid in the flask was cooled and filtered, since some more sodium chloride forms due to the heat and incompletion of the reaction in the previous refluxing. It was attempted to separate the crude benzyl cyanide by using a long narrow 1-liter separatory funnel. As the specific gravity of benzyl cyanide is 1.014, one would expect to have some difficulty separating it from water and such is the case. At least one would expect to find the layer of benzyl cyanide on the bottom, but it was found that this was not the case. It was always found in the upper half of the liquid in the separatory funnel However all of the liquid was distilled under diminished pressure and what little was found in the lower layer in this case, twenty-five grams (25 g.) was combined with the one-hundred and thirty-five grams (135 g.) obtained from the upper half of the liquid. The distilling flask used was a Claisen side-arm distilling flask and the benzyl cyanide was collected at 136 to 140°C at fifty millimetres of mercury pressure. The alcohol comes over first below 80°C at 50 mm. and the water next below 70°C at 50 mm. and finally the benzyl cyanide. In later experiments it was also collected at 115 to 120°C at 10mm. The yields all ran very close to seventy per cent of the theoretical.

The product on the first distillation was usually of a light color. Redistillation gave a clear colorless product which in all cases was used in subsequent preparations, since the purity of the product was essential. The specific gravity was 1.014 and is another means of identification.

(3) Phenylacetic methylester, $C_6H_5CH_2CO_2CH_3$, was prepared four times as directed by M. Rising and J. Stieglitz[6] who in general followed the directions of Wislicenus[15] for the preparation of the ethyl ester.

$$\underset{\text{Benzyl cyanide}}{C_6H_5CH_2CN} + CH_3OH + H_2O \xrightarrow{HCl} NH_4Cl + \underset{\text{Phenylacetic methylester}}{C_6H_5CH_2CO_2CH_3}$$

The materials taken were as follows:

Benzyl cyanide.....100 g.

Absolute methyl alcohol..... 200 g.

Water..... 20 g.

Rock salt (NaCl).....500 g.

Hydrochloric acid (Technical) concentrated.....200 c. c.

Sulfuric acid...(Technical) concentrated.....1000 c.c.

To two hundred grams (200 g.) of absolute methyl alcohol, (later experience showed that commercial 97% methyl alcohol would serve just as well), were added 100 g. of benzyl cyanide and twenty grams of water. The 1-liter round bottom pyrex flask containing these liquids was placed under reflux and dry hydrogen chloride gas was passed into the mixture at a rapid rate. The solution became hot without heating, and after the gas passed in for half an hour, a heavy white flocculent precipitate of ammonium chloride settled out during the course of a rather violent reaction, that is, rapid refluxing of alcohol therein. The treatment with HCl gas was continued to saturation, first without cooling, and then

with the receiving vessel surrounded by ice. It was thought advisable to allow the mixture to stand for an hour in the flask surrounded by ice and then to pass HCl gas for a short time again, when the mixture was absolutely cold. The passing of gas was stopped when it was no longer absorbed.

The flask was allowed to stand twenty-four hours and then, while still connected to the reflux condenser, heated in a water bath for a period of one hour to drive off excess HCl gas.

The mixture was cooled and 300 g. of ether added and finally just sufficient water to dissolve the ammonium chloride. The ether solution was separated and washed with 10 c.c. portions of 0.1 normal sodium carbonate solution until the aqueous solution removed was alkaline. Care must be used to wash the ether solution of the ester with only small amounts of sodium carbonate to avoid hydrolysis of the ester. The alkali must be separated quickly and completely from the ether solution. All the wash waters were combined, filtered, and dried over anhydrous calcium chloride for a period of at least eight hours. The liquid remaining after evaporation of the ether was fractionated. The yield of ester of boiling point 212 to 218° C was one hundred and eighteen grams or 96% of the theoretical yield.

In all cases, when the preceding directions were followed, the yields were all at least ninety per cent of the theoretical. Theoretically and practically the esterification method of Emil Fischer[24] is more convenient. This consists of the use of concentrated sulfuric acid. It appears, however, that the yields cannot be improved over those obtained by Wislicenus' method.

(3) Dimethyl oxalate, $(COOCH_3)_2$. Vanino's[22] method for the preparation of dimethyl oxalate was modified by Rising and Stieglitz[6] and the following far simpler method was used with better results.

$$\begin{matrix} COO(H \\ | \\ COO(H \end{matrix} + \begin{matrix} HO)CH_3 \\ \\ HO)CH_3 \end{matrix} \xrightarrow[gas]{HCl} \begin{matrix} COOCH_3 \\ | \\ COOCH_3 \end{matrix} + 2H_2O$$

The materials used:

Anhydrous oxalic acid.....300 g.

Absolute methyl alcohol.....378 g.

Technical concentrated hydrochloric acid.....100 c.c.

Technical concentrated sulfuric acid.....1000 c.c.

Rock salt.....500 g.

The 300 g. of anhyrous oxalic acid were prepared by heating oxalic acid, with two molecules of water of crystallization, in shallow evaporating dishes in a warm oven (temperature equal to 95° C) for several days. To the 300 g. of anhydrous oxalic acid was added 378 g. of absolute methyl alcohol and the mixture was placed under reflux and dry HCl gas was passed into it in a strong stream. The mixture quickly became hot and the receiving vessel was then cooled with ice to prevent decomposition of the ester. White crystals of methyl oxalate came out slowly after dry HCl gas had been passed in for at least 2 hours and a solid mass of crystals filled the flask at the end of 4 hours. The flask and contents were left standing 24 hours, and the crystals were then filtered on a Buchner funnel and kept over suction for 6 hours to remove the odor of the HCl gas. The crystals were then placed in a vacuum desiccator and dried for 3 days to remove last traces of HCl. Melting point of crystals was 52.0 to 55° C. The yield was 285 g. or 72% of the theoretical yield.

Dimethyl oxalate was prepared a second time according to the directions of E. Bowden[28] this method possesses the following advantages: (1) more convenient; (2) cheaper, (3) greater yield, and (4) better product.

The method is really Emil Fischer's method of esterifying.

In a 2-liter round-bottom Pyrex flask, fitted with a cork which loosely carried a water-driven mechanical stirrer and a separatory funnel, were placed 270 g. of anhydrous oxalic acid and 300 c.c. of absolute methyl alcohol. Then while the mixture was rapidly stirred, 105 c.c. of C.P. 98% sulfuric acid was added slowly through the separatory funnel. The mixture was heated nearly to boiling and then filtered as rapidly as possible in a hot water funnel. The first flask was rinsed out with 120 c.c. of hot absolute CH_3OH and poured through the filter paper. After 24 hours at 15° C the crystals were filtered with suction on a Buchner funnel, sucked dry as possible, pressed between filter paper, and air dried for a few minutes. The filtrate was cooled to -6° C and another batch of crystals obtained and treated as the others. They were recrystallized by dissolving in 300 c.c. of hot 97% methyl alcohol, filtering, and allowing to crystallize. After several hours the crystals were filtered off and the filtrate cooled to obtain another batch of crystals. A total of 230 g. or 90% of the theoretical yield was obtained, m.p. 53.5° C.

The absolute methyl alcohol used in these preparations was prepared as follows: To 1-liter of 97% methyl alcohol were added 200 to 300 g. of stick potash (KOH). The mixture was heated under reflux for 3 hours, allowed to stand over night, filtered from the KOH. To the alcohol was then added 200 to 300 g. of powdered quick-

lime (CaO). It was again heated under reflux for 3 hours, allowed to stand overnight and the alcohol distilled directly from the slaked lime ($Ca(OH)_2$).

(4) Sodium oxalylphenylacetic dimethylester, $CH_3O_2CC(ONa)=C(C_6H_5)(CO_2CH_3)$, was prepared four times.

Materials used:

Phenyl acetic methyl ester..... 50 g.
Sodium wire (1.0 mm. in diameter)..... 8 g.
Ether (dried over sodium).....160 g.
Absolute methyl alcohol..... 20 drops
Methyl oxalate..... 40 g.

To 165 g. of sodium dried ether were added 8 g.of sodium wire and 40 g. of methyl oxalate. The oxalate dissolves only partially. There were then added 25 g. of phenylacetic methyl ester and 10 drops of absolute methyl alcohol. The 1-liter round-bottom Pyrex flask was placed at once under reflux. Bubbles of gas were given off immediately, apparently hydrogen, since it originated from around the sodium wire. Five hours later yellow crystals appeared on the sodium wire. The next day an abundant yellow precipitate appearedin the ethereal solution, that is, a mass of yellow crystals covered the bottom of the flask. The liquid above the yellow mass was a dark red color. Two days were allowed for the completion of the reaction and at the end of that time the mixture was heated for one hour on a water bath while under reflux to make sure that the reaction had gone to completion. The contents of the flask were allowed to cool and the precipitate was filtered on a Buchner funnel, washed with dry ether, and dried in vacuo. Yield was 70 g. or 81% of theoretical.

(5) Oxalyl phenylacetic dimethylester, $CH_3O_2CCOCH(C_6H_5)CO_2CH_3$, was prepared by treating the sodium salt of oxalyl phenyl acetic dimethyl ester with cold dilute sulfuric acid. The directions at this stage were quite general, so the amount of sulfuric acid used was based upon 100% reaction. A cooled mixture of 30 g. of pure sulfuric acid and 300 g. of water were added to 65 g. of sodium oxalyl phenyl acetic dimethyl ester. After much stirring for a period of 1 hour a heavy dark brown layer was formed. The mixture was extracted with ether and the ether extract dried over anhydrous calcium chloride.

After evaporation of the ether the ester was decomposed in vacuo in the manner described by Wislicenus.[7] The ester when warmed at 117°C. and 17 mm. showed evidence of decomposition, with evolution of a gas, and a change of color of the liquid from bright red to dark brown. The manometer showed a decided increase in pressure, and bubbles of the gas were ignited and burned with a blue flame characteristic of carbon monoxide. When the loss of carbon monoxide was complete, the pressure fell rapidly to the original 17 mm.

(6) Phenylmalonic dimethylester, $C_6H_5CH(CO_2CH_3)_2$, was obtained by continuing the distillation as described in (5), until the thermometer rose to 150°C. The small fraction of impure ester passing over below this was collected separately. The main fraction was collected between 160 to 195°C. and this crystallized as a mass of yellow needle crystals.

The solid mass of crystals was purified by dissolving in hot boiling ligroin and allowing the ligroin to evaporate spontaneously. The yield of pure white crystals in the form of rosets, m.p. 48°C., was 41 g. or 85% of theoretical.

(7) Ethyl phenylmalonic dimethyl ester, $(CH_3O_2C)_2C(C_6H_5)$-(C_2H_5) was attempted five times.

Materials used:

Methyl alcohol (absolute).....30 g.

Sodium (in small pieces)..... 3 g.

Phenyl malonic methyl ester.....30 g.

Ethyl iodide.....30 g.

The sodium methylate was prepared from 30 g. of absolute methyl alcohol and 3 g. of sodium. To this solution, 30 g. of phenyl malonic dimethyl ester were added, and the 500 c.c. round-bottom Pyrex flask was placed under reflux. A white precipitate formed which is the sodium salt of the phenyl malonic dimethyl ester. 30 g. of ethyl iodide were added in small portions through the condenser tube. There was no apparent reaction, and it was necessary to heat the mixture for 4 days on a steam bath to bring about ethylation. That the reaction did not go to completion in all of the 5 trials was shown by the fact that the mixture remained alkaline. At this point Rising and Stieglitz modified the directions of Conrad and Limpach[24] with good results. They claimed that, before proceeding further it was necessary to neutralize the mixture by the addition of a few drops of cold dilute sulfuric acid. Enough water was then added to dissolve the sodium iodide formed in the reaction, and to cause the ethylated ester to separate as a non-miscible layer at the bottom of the flask. The ester layer was separated from water above it, and dried over anhydrous calcium chloride. The aqueous layer contained a small amount of the ester, and was extracted twice with ether, and the ether solution dried over anhydrous calcium chloride.

After evaporation of the ether, the remaining liquid, which was dark red in color, was added to the main portion, and distilled in vacuo.

From 120 to 130°C., at 17 mm., there was obtained a dark red liquid and some iodine fumes were formed. The change was complete below 132°C. and a brown liquid remained in the Claisen side-arm distilling flask. From 155 to 162°C., a fraction of impure ethylated ester was obtained, and from 175 to 188°C., the main fraction distilled. This was allowed to stand overnight but no solidification occurred as was expected.

The fractions were combined and distilled again in vacuo, and new fractions were collected at 10 to 100°C., 100 to 135°C., 135 to 157°C., and 157 to 177°C., all at 17 mm. None of these crystallized. Rising and Stieglitz stated that the fraction of high boiling point crystallizes when cooled, and remains solid at room temperature. Fraction of low boiling point crystallizes slowly on cooling but softens somewhat at room temperature. The yield of crude product (m.p. 33°C.) was 26 g. or 76% of theoretical.

By recrystallization from ligroin crystals were obtained with melting point of 37°C. Crystals are large, colorless, and transparent.

There were two instances in the five preparations that were made in which the final products crystallized when cooled to below 0°C. for a considerable length of time. At room temperature, however, the crystals melted showing that they were impure.

The ethylation of phenyl malonic dimethylester in an alcoholic solution according to the above leads to not altogether satisfactory yields as a result of saponification and decomposition of ester, exactly as observed by Wislicenus for the ethylester. Rising and Stieglitz suggest the preparation of the dry sodium salt of

phenyl malonic methyl ester and treating the dry sodium salt in an autoclave which they hoped would compensate the method by giving an increased yield. However the results were not satesfactory and they state that more experiments will be carried out in the autoclave with different higher temperatures.

Cretcher and Nelson[10] also stated that ethylation in an alcoholic solution is attended by decomposition of the ester. They worked with phenyl malonic diethyl ester and the production of ethyl phenyl malonic diethyl ester. It was observed by them that in case an excess of sodium was used the decomposition was practically complete. They ethylated successfully by heating the dry sodium salt of the ester with ethyl bromide in a sealed tube at 110°C. without a solvent.

It was observed in this laboratory that the ethylation of the ester can be carried out successfully by adding 200 c.c. of absolute ether to the flask at the start of the reaction. The same quantities of the other materials were used and the same procedure was followed as before. In this case the ethylation goes nearer to completion and gives the product stated by M. Rising and J. Stieglitz.[6] The presence of the ether allows the reaction to take place at a lower temperature and this, it is believed, explains the success of the reaction. A pure product, m.p. 38°C., was obtained which was 62% of theoretical. The yield of crude product was 85% as compared with 76% obtained by Rising and Stieglitz. They do not state their yield of final pure product.

(8) "Luminal", $(C_6H_5)(C_2H_5)\overline{CCONHCONHCO}$, was prepared successfully once by this method.

Materials used:

Ethyl phenyl malonic dimethyl ester.....2.5 g.

Urea (c.p.).....1.1 g.

Sodium.....0.9 g.

Absolute methyl alcohol.....14.2 g.

Sodium methylate was prepared from 14.2 g. of absolute methyl alcohol and 0.9 g. sodium in a 200 c.c. pressure flask. To it were added 2.5 g. of ethyl phenyl malonic dimethyl ester and 1.1 g. of urea. The mixture was heated in the pressure flask in a saturated solution of salt to a temperature of 105 to 108° C. for six hours. The use of pressure flask is a modification of their procedure and gives more freedom in its use in the laboratory. When the flask had cooled, a white precipitate (chiefly sodium carbonate) was removed and washed with absolute methyl alcohol. The filtrate was again heated for 6 hours at a temperature of 105 to 108° C. Any further precipitate was removed as before. The filtrate which was alkaline, was neutralized with acetic acid , and the alcohol evaporated in vacuo. When the last of the alcohol was gone, the residue in the distilling flask had an oily appearance, and when a few c.c. of water were added, a cloudy emulsion was formed. This emulsion was extracted with ether and the ether allowed to evaporate spontaneously. The residue was a thick viscous liquid which on cooling, yielded no crystals as stated by them. It was thought that the experiment was a failure but, on extracting the thick liquid with boiling water and pouring off the aqueous layer a crystalline deposit of "Luminal" was obtained on cooling. The crystals were extracted with ligroin to remove any unchanged ester occluded by the crystals.

The crystals were recrystallized from boiling water and gave a melting point of 172 to 174° C. A yield of one gram, equivalent to 40 % of theoretical, was obtained.

II. The Preparation of "Luminal" by means of the Ethyl Ester according to the method of Rising and Stieglitz.[6]

It is obvious that, in the method of Rising and Stieglitz, it may be possible to use the ethyl ester of ethyl phenyl malonic acid in place of their methyl ester. The reactions involved are those already given on pages 11 to 14.

Procedure

(1) Phenylacetic ethylester, $C_6H_5CH_2CO_2C_2H_5$, was prepared twice according to the directions of Wislicenus.[15]

$$\underset{\text{Benzyl cyanide}}{C_6H_5CH_2CN} + C_2H_5OH + H_2O \xrightarrow{HCl} NH_4Cl + \underset{\text{Phenylacetic ethylester}}{C_6H_5CH_2CO_2C_2H_5}$$

Materials used:

Benzyl cyanide.....100 g.

Absolute ethyl alcohol.....200 g.

Water.....80 g.

Rock salt (NaCl).....500 g.

Hydrochloric acid (Technical).....200 c.c.

Sulfuric acid (Technical).....1000 c.c.

The details of the procedure are the same as given on page 16 for the preparation of phenylacetic methylester.

The yield was 100 g. or 80 % of theoretical. The boiling point of the ester was 140 to 142° C., at 60 mm.

(2) Sodium oxalylphenylacetic diethylester, $C_6H_5O_2CC(ONa)=C(C_6H_5)(CO_2C_2H_5)$, was prepared twice according to the directions of Wislicenus.[19]

Materials used:

Diethyl oxalate.....10 g.

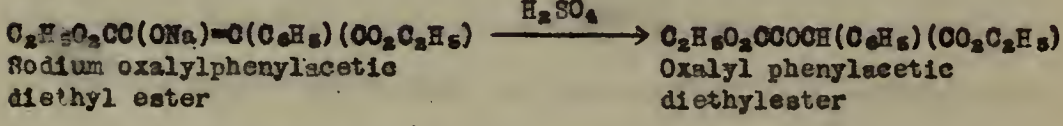
Sodium wire.....(1 mm. in diameter).....3.2 g.

Ether.....(dried over sodium).....40 g.

Phenylacetic ethylester.....12 g.

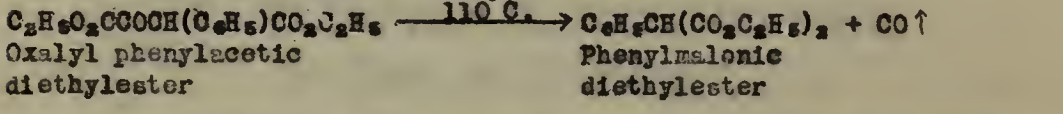
The details of the procedure are the same as given for the preparation of sodium oxalylphenylacetic dimethylester on page 20.

(3) Oxalylphenylacetic diethylester, $C_2H_5O_2CCOCH(C_6H_5)(CO_2C_2H_5)$, was prepared twice by the same treatment used for the methyl ester on page 21.



Sodium oxalylphenylacetic diethyl ester — Oxalyl phenylacetic diethylester

(4) Phenylmalonic diethylester, $C_6H_5CH(CO_2C_2H_5)_2$, was prepared twice in the manner described on page 21.



Oxalyl phenylacetic diethylester — Phenylmalonic diethylester

A yield of 5 g., equivalent to 33% based upon the phenyl acetic ethyl ester, was obtained boiling between 155 to 157° C., at 9 mm. The identification of the compound was completed by comparison of the boiling point with the observations of Ruhemann[25] and Packard and Yates.[26]

(5) Ethylphenyl malonicdiethyl ester, $(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2$, was prepared once in the modified manner described on page 24.

$$C_6H_5CH(CO_2C_2H_5)_2 + C_2H_5I \xrightarrow[(C_2H_5)_2O]{NaOCH_3} (C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2$$

Phenylmalonic diethylester — Ethyl phenylmalonic diethylester

Materials used:

Phenyl malonic diethyl ester..... 25 g.

Sodium.....2.5 g.

Ethyl iodide..... 25 g.

Ether (dried over sodium).....200 c.c.

Absolute methyl alcohol..... 25 g.

A yield of 16 g., equivalent to 60% of theoretical, was obtained boiling between 150 to 160° C., at 12 mm. The boiling point observed does not agree with that given in patents.[9]

The ethyl phenyl malonic diethyl ester could be condensed with urea as described in detail on page 25. This particular ester was the one used in the commercial synthesis[2] in this country before the World War.

III. The Preparation of "Luminal" according to Wm. Nelson and R. Cretcher.[10]

This study led to some very interesting observations as described in the following paragraphs. The method of Nelson and Cretcher is as follows: (1) The condensation of benzyl cyanide with diethyl carbonate. The method of Hessler[18]—sodium as a condensing agent, in ether—was repeated with good results. The reaction is on page 6.

(2) The conversion of phenyl cyanoacetic ethyl ester to phenyl malonic diethyl ester. This is effected with dry hydrogen chloride gas and ethyl alcohol according to Wislicenus[16]. The nitrile compound is practically impossible to separate from the desired ester owing to the fact that their boiling points are only three degrees apart.

The investigation resulted in obtaining phenyl malonic diethyl ester in very pure form. It crystallized when cooled to 10°C. and had a melting point of 18 to 19°C. This has not been previously observed.

Another interesting observation was made with the crude product of phenyl malonic diethyl ester which at this stage was a liquid. The crude product contained some crystals which would not cause the crude product to crystallize when cooled. The crystals were separated and found to be insoluble in ether, but soluble in alcohol and benzene, indicating very much that it was an amide. Recrystallization of the amid , which later investigation proved it to be, gave a melting point of 124 to 125°C. This melting point does not agree with the melting point of the phenyl malonic ethyl ester mono-amid observed by Wislicenus[17] to be 154°C.

The phenyl malonic diethyl ester and the phenyl malonic ethyl ester mono-amid obtained in this procedure are purer than the products obtained by the method of Wislicenus because the product obtained by the latter is more apt to be contaminated with impurities due to the method used for synthesis.[7]

The main reaction is given on page 7. The side reaction takes place as follows:

$C_6H_5CH(CN)(CO_2C_2H_5) + C_2H_5OH \xrightarrow{HCl} C_6H_5CH(CO_2C_2H_5)(C{=}NH_2ClOC_2H_5)$

Phenyl cyanoacetic ethylester

Phenyl malonic mono-ethyl ester ethylimidoesterhydrochloride

$\downarrow -C_2H_5Cl$

$C_2H_5Cl + C_6H_5CH(CO_2C_2H_5)(CONH_2)$

Phenyl malonic ethyl ester mono-amide

(3) The ethylation of phenyl malonic diethyl ester and the condensation with urea were carried out according to the modified procedures given on pages 24 and 25. The ethyl phenyl malonic diethyl ester was again (page 28) observed to boil between 152 to 158°C., at 11 mm.

Procedure

(1) Diethyl carbonate, $(C_2H_5)_2CO_3$, was prepared once according to Clermont.[27]

$Ag_2CO_3 + 2C_2H_5I \longrightarrow 2AgI + (C_2H_5)_2CO_3$

Silver carbonate; Ethyl iodide; Diethyl carbonate

Materials used:

Silver nitrate.....50 g.

Sodium carbonate.....18 g.

Ethyl iodide.....30 g.

Ethyl alcohol (95%).....10 c.c.

To 50 g. of silver nitrate in an aqueous solution were added 18 g. of sodium carbonate. Immediately a white precipitate of silver carbonate was formed. The silver carbonate was washed with a few c.c. of alcohol and sucked dry as possible on a Buchner funnel.

It was then dried and transferred to a 200 c.c. round-bottom Pyrex flask connected with a reflux. Through the condenser tube were added 30 g. of ethyl iodide. The mixture was warmed sufficiently to cause gentle refluxing for three days and at the end of that time the reaction seemed complete. The flask was cooled and the contents extracted with absolute ethyl alcohol, the alcohol was distilled off first and then the liquid collected from 100° to 126°C. A yield of 9 g. or equivalent to 60% of theoretical, was obtained.

(2) Phenyl cyanoacetic ethylester, $C_6H_5CH(CN)(CO_2C_2H_5)$, was prepared three times.

Materials used:

Ethyl carbonate..... 56 g.
Sodium wire (1mm. in diameter).....10.9 g.
Sodium dried ether.....350 c.c.
Benzyl cyanide..... 56 g.

10.9 g. of sodium in wire form (1 mm. in diameter) were put into a solution of 56 g. of diethyl carbonate in 350 c.c. of absolute ether. There was only slight reaction for a moment which subsided quickly. Then 56 g. (the theoretical amount) of benzyl cyanide were added in small portions through the condenser tube into the 1-liter round-bottom Pyrex flask which was under reflux. Hydrogen began to escape at once and the sodium wire became golden yellow. The temperature soon rose to the boiling point of ether. consequently the flask was kept cooled by means of running water, until the greater part of the sodium had gone into solution. The mixture was allowed to stand 12 hours under reflux. The reaction product separated out as a yellow solid and the supernatant layer of ether was brown in color.

Cold dilute sulfuric acid (30 g. of H_2SO_4 in 255 g. of H_2O, based upon a 70% yield of the sodium salt of phenyl acetic ethyl ester) was added and the yellow solid went into solution. The ethereal layer was separated, washed with water, and dried over anhydrous calcium chloride overnight. After the distillation of the ether a brown liquid remained. This was distilled at reduced pressure (12 mm.) with the following result:

Fraction	Temperature	Weight
1	0-115°C.	3 g.
2	115-190°C.	55 g.

5 g. of residue remained in the distilling flask. A redistillation of fraction 2 gave the following result:

Fraction	Temperature	Weight
1	0-115°C.	2 g.
2	115-150°C.	7 g.
3	150-180°C.	45 g.

Fraction 3 boiled at 161°C. at 12 mm. most of the time. It was a 50% yield, although 55% was obtained by Hessler.

The method described gave a pure clear colorless product each time it was prepared. It is a more convenient laboratory preparation than the method of Bodroux[14] which gives a 70% yield.

(3) Phenyl malonic diethylester, $C_6H_5CH(CO_2C_2H_5)_2$, was prepared in the same manner as described on page 16.

Materials used:

Phenyl cyanoacetic ethyl ester..... 45 g.

Ethyl alcohol (95%).....100 g.

Rock salt.....250 g.

Technical concentrated sulfuric acid.....500 c.c.

Technical concentrated hydrochloric acid.....100 c.c.

A yield of 35 g., equivalent to 62% of theoretical, was obtained boiling between 150 to 172°C., at 12mm., and giving a m.p. of 18 to 19°C.

(4) Ethyl phenyl malonic diethyl ester, $(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2$, was prepared twice in the modified manner described on page 24.

Materials used:

Phenyl malonic diethyl ester..... 30 g.
Sodium (in small clean pieces)..... 30 g.
Ether (dried over sodium).....200 c.c.
Ethyl iodide..... 30 g.
Absolute methyl alcohol..... 30 g.

A yield of 20 g., equivalent to a 62% of theoretical, was obtained boiling between 152 to 158°C., at 11 mm.

(5) "Luminal", $(C_6H_5)(C_2H_5)\overline{CCONHCONH}CO$, was prepared according to directions on page 25.

Materials used:

Absolute methyl alcohol.....14.2 g.
Sodium (in small clean pieces)..... 0.9 g.
Urea..... 1.1 g.
Ethyl phenyl malonic diethyl ester..... 2.5 g.

The yield was 1 g. or about 40% of the theoretical yield. The crystals were purified by recrystallization from boiling water, and after two recrystallizations, the product showed a melting point of 174°C. The crystals are pure white, and lustrous. The reaction is given on page 1.

IV. The Preparation of the Amides of Phenyl Malonic Acid

The phenyl malonic ethyl ester mono-amide and the phenyl malonic diamide were prepared by heating phenyl malonic diethyl ester with alcoholic ammonia in a pressure flask at a temperature of about 105 to 108°C. according to the method of Wislicenus.[17] The reactions are given on page 8.

The phenyl malonic ethyl ester mono-amid after two recrystallizations gave a sharp melting point of 124 to 125°C. as observed on page 29. This is in disagreement with the observations of Wislicenus[17] who gave it a melting point of 154°C. The phenyl malonic diethyl ester used in this synthesis was very pure as stated on page 29, since it was definitely crystalline. However the ester which was used by Wislicenus was impure due to his method of synthesis. Wislicenus mentioned that it was difficult to obtain the phenyl malonic diethyl ester in pure state and this was confirmed by Rising and Stieglitz.[6] Consequently Wislicenus was only able to obtain a product which he thought was the mono-amide and another product (diamide?) which he stated sublimed. He was not able to obtain enough of the second product to make an analysis of it.

This investigation, instigated out of curiosity of what the crystals could be that were found with the phenyl malonic diethyl ester as stated on page 29, gave us two products with sharp melting points and also enough of each for analysis of its constituents. The melting points for the phenyl malonic ethyl ester mono-amide and the phenyl malonic diamide were respectively 124 to 125°C. and 228 to 230°C. Analysis for nitrogen in the two compounds gave results which were within 1% of the calculated values.

Procedure

To 7 g. of phenyl malonic diethyl ester (m.p. 19 °C.) in a 200 c.c. pressure flask were added 150 c.c. of absolute ethyl alcohol saturated with ammonia gas. The flask was clamped and heated in a brine bath, at a temperature of about 108°C. for seven hours. On the inside of the neck of the pressure flask had sublimed some crystals which were removed and found to be quite volatile. In fact attempts to determine its melting point showed that crystals sublimed instead of melting. The crystals might possibly be ammonium carbonate formed by the ammonia and carbon dioxide in the flask which was under pressure. This product seems to be the one considered by Wislicenus to be the diamide.

The alcoholic solution was removed from the pressure flask and evaporated to dryness. The remaining white crystals were extracted with small portions of boiling benzene. A white mass of crystals remained undissolved in the benzene, but they were easily extracted with boiling absolute ethyl alcohol. The benzene, on cooling, yielded white lustrous crystals.. And after a second recrystallization, from boiling benzene, a 2 g. yield of the product (mono-amide?) showed a melting point of 124 to 125°C. The alcohol, on cooling, yielded white crystalline product which after a second recrystallization gave a 1.5 g. yield of the product (diamide?), m.p. 228 to 230°C.

Identification of the Above Products

The compounds were analyzed for nitrogen by the Kjeldahl method.

The analysis for phenyl malonic ethyl ester mono-amide, $C_{11}H_{13}O_3N$ or $C_6H_5CH(CONH_2)(CO_2C_2H_5)$.

	I	II
Weights of sample taken	0.4999 g.	0.5014 g.
% Nitrogen found	7.4416 %	7.4398 %
% Nitrogen calculated from formula	6.7632 %	6.7632 %

The analysis for phenyl malonic diamide, $C_9H_{10}O_2N_2$ or $C_6H_5CH(CONH_2)_2$.

	I	II
Weights of sample taken	0.2141 g.	0.2138 g.
% Nitrogen found	15.694 %	16.098 %
% Nitrogen calculated from formula	16.667 %	16.667%

V. The Preparation of 5,5-Isoamyl Phenyl Barbituric Acid

Isoamyl phenyl malonic diethyl ester and a new barbituric acid, 5,5-Isoamyl phenyl barbituric acid, have been synthesized for the first time. Time did not permit complete identification of the two compounds.

Procedure

(1) Isoamyl phenyl malonic diethyl ester, $(C_6H_5)(C_5H_{11})C(CO_2C_2H_5)_2$, was prepared twice in the modified manner described on page 24 for the alkylation of malonic esters.

Materials used:

Phenyl malonic diethyl ester.....30 g.

Isoamyl iodide (b.p. 18 to 19°C.).....35 g.

Ether (dried over sodium).....200 c.c.

Absolute methyl alcohol.....30 g.

Sodium (in small pieces).....3 g.

A yield of 19.5 g., equivalent to 50 % of theoretical, was obtained boiling between 160 to 180°C., at 19 mm. It was a colorless liquid and boiled chiefly at 187 to 188°C.(19 mm.); $d_{20}^{20} = 1.0642$.

(2) 5,5-Isoamyl phenyl barbituric acid, $(C_6H_5)(C_5H_{11})CCONHCONHCO$, was prepared twice according to the modified procedure on page 25.

Materials used:

Isoamyl phenyl malonic diethyl ester.....2.5 g.

Urea.....0.9 g.

Absolute ethyl alcohol.....11.0 g.

Sodium.....0.7 g.

A yield of 0.35 g., equivalent to 10 % of theoretical, was obtained. After two recrystallizations from boiling water, the product showed a melting point of 162 to 164°C. The crystals were needle-like, pure white, and lustrous.

VI. The Condensation of Bromomalonic Diethyl Ester and Benzene.

It was first attempted to condense bromomalonic diethyl ester and benzene with anhydrous aluminum chloride as the condensing agent.

The condensation was tried, under varying conditions, in excess benzene, carbon disulfide, ligroin, petroleum ether, and nitrobenzene. The reaction is given on page 9.

In all the reactions, except when petroleum ether was used, condensation seemed to be effected. But at best it was not possible to obtain a yield greater than 20 %, probably due to decarboxylation of the malonic ester.

$C_6H_5CH(CO_2C_2H_5)_2 \longrightarrow CO_2\uparrow + C_6H_5CH(C_2H_5)(CO_2C_2H_5)$

Phenylmalonic diethylester — Ethylphenylacetic ethylester

This may explain the greater yield of a lower boiling product, not desired.

However no positive proof was obtained that the 20 % yield mentioned above was the desired ester, although the boiling point of the product obtained compared well with the boiling point of phenyl malonic diethyl ester.

The condensation was later attempted with zinc dust as the condensing agent. Some sort of condensation was effected. The product obtained was not the desired one, because it did not have the properties of phenyl malonic diethyl ester. Other interests did not allow a further study of what was obtained.

Procedure

(1) Bromomalonic diethyl ester, $(Br)(H)C(CO_2C_2H_5)_2$, was prepared twice according to directions of C.S.Palmer.[25]

$H_2C(CO_2C_2H_5)_2 + Br_2 \xrightarrow{CCl_4} HBr\uparrow + (Br)HC(CO_2C_2H_5)_2$

Malonic diethyl ester — Bromo-malonic diethylester

Materials used:

Malonic diethyl ester.....160 g.

Bromine liquid dried with sulfuric acid.....165 g.

Carbon tetrachloride.....150 c.c.

A 1-liter 3-necked flask was fitted with a stirrer, and with a reflux condenser with a tube leading to a flask of water for absorption of hydrogen bromide gas, and a separatory funnel with a stem drawn to a fine tip which reaches almost to the blades of the stirrer. In the flask was placed 160 g. (1 mole) of malonic diethyl ester and 150 c.c. of carbon tetrachloride. In the separatory funnel were placed 165 g. (1.03 moles) of dry liquid bromine. The stirrer was started, and a few c.c. of bromine was run into the solution. The flask was warmed with a small flame until reaction started. Then the rest of the bromine was added gradually at such a rate as to keep the liquid boiling gently. It was then refluxed until no more hydrogen bromide was evolved (about 2 hours). The mixture was then cooled and washed five times with 50 c.c. portions of a 5% sodium carbonate solution. It was then distilled under reduced pressure (20 mm.), fractions being taken up 130°C., and at 130 to 150°C. The residue amounted to about 10 g. The two fractions were combined and redistilled again under the same reduced pressure. 200 g. of product, equivalent to 88% of theoretical, was obtained boiling between 130 to 134°C.

(2) Aluminum chloride, $AlCl_3$, was used as in the general Friedel-Crafts' reaction.

Materials used:

Benzene.....25 g.

Aluminum.Chloride.....50 g.

Bromo-malonic diethyl ester.....25 g.

Solvents used: (Excess benzene, petroleum ether,
ligroin, carbon disulfide, and nitrobenzene....100 g.

In all these reactions, anhydrous reagents were used.

A 500 c.c. 3-necked flask was fitted with a stirrer, a reflux condenser with a tube extending to a flask of water for absorption of hydrogen bromide generated, and the third neck was reserved for the addition of the aluminum chloride. In the flask were placed 25 g. of bromo-malonic diethyl ester, and 100 g. of benzene. The stirrer was started and 30 g. of aluminum chloride in small portions were added during a course of half an hour. The aluminum chloride on striking the liquid turned from yellow to green and finally to a black pasty mass. On heating the flask with a hot water bath (temperature about 85°C.) bubbles of gas were given off. The gas collected in the absorption bottle was tested with silver nitrate and a yellow precipitate of silver bromide indicated that hydrogen bromide was being evolved. After all the aluminum chloride was added, the mixture was refluxed until no more hydrogen bromide was evolved (about 2 hours). The mixture was allowed to stand over-night and the next morning the excess benzene was distilled off. To the flask were added 300 g. of chipped ice to decompose the aluminum chloride remaining in the thick black liquid. 10c.c. of concentrated hydrochloric acid were added to keep the aluminum chloride in solution and then the mixture was steam-distilled for about 15 minutes to drive off any benzene. To the flask were added 150 g. of ether. The ether layer was separated and the aqueous solution again was extracted with small portions of ether. All ether solutions were combined and made neutral with dilute sodium carbonate solution. The ether layer was dried over anhydrous calcium chloride for a period of eight hours.

The ether was then distilled off and the residue distilled under reduced pressure (15 mm.) with following result: 7 g. of a product boiling between 105 to 110°C and 2 g. of a product boiling between 150 to 172°C. The yield of high boiling product was 20% of the theoretical yield.

(2) Zinc dust, Zn, was used as the condensing agent to see whether the yield could be increased over that obtained in the previous procedure.

Materials used:

Bromomalonic diethyl ester..... 68 g.

Benzene.....300 g.

Zinc dust..... 30 g.

Hydrochloric acid (concentrated)..... 50 c.c.

A 1-liter 3-necked flask was fitted with a stirrer, a reflux condenser with a tube extending to a flask of water for absorption of hydrogen generated, and the remaining neck was reserved for the addition of the zinc dust. In the flask were placed 68 g. of bromo-malonic diethyl ester and 300 g. of benzene. The stirrer was started and 30 g. of zinc dust were added in small portions during the course of half an hour. The mixture was heated slightly to keep the mixture refluxing gently. When the evolution of hydrogen appeared complete, the excess benzene was distilled off. The unused zinc was filtered off and the filtrate was steam-distilled to drive off any benzene. 50 c.c. of concentrated hydrochloric acid were added to convert any zinc hydroxide to zinc chloride. Th eolution was extracted with ether. The ether solution was washed several times with dilute portions of 0.1 M. sodium carbonate solution until neutral and finally washed with water.

The ether layer was separated and dried over anhydrous calcium chloride over night. The ether was distilled and the residue fractionated under reduced pressure (14 mm.) with the following result:

Fraction	Temperature	Weight
1	0-150°C.	5 g.
2	150-220°C.	3 g.
3	220-260°C.	50 g.

A redistillation of fraction 3 gave the same result in smaller quantity, that is, it was collected at the same temperature.

VII. The Condensation of Malonic Diethyl Ester and Phenetole

The condensation of phenetole (phenyl ethyl ether) and malonic diethyl ester, under varying conditions, was attempted with phosphorous pentoxide and anhydrous zinc chloride as condensing agents. The hoped-for reaction is given on page 9.

Phosphorus pentoxide caused some very interesting color changes, probably due to the formation of an addition compound. However the final purple product returned to its original constituents on distillation. The condensation seemed to be effected in small quantity (10%) with anhydrous zinc chloride. However, no positive proof was obtained to indicate that it was the desired compound. Nevertheless it was the yields that discouraged any further investigation of the condensation.

Procedure

(1) Phenetole, $C_6H_5OC_2H_5$, was prepared in general according to the Williamson synthesis.[29]

$C_6H_5O(Na + I)C_2H_5$ ——— $C_6H_5OC_2H_5 + NaI$

Materials used:

Absolute ethyl alcohol.....300 c.c.

Sodium (in small clean pieces)..... 23 g.

Phenol..... 94 g.

Ethyl iodide.....195 g.

To 300 c.c. of absolute ethyl alcohol were added 23 g. of sodium in small pieces, the flask was immediately placed under reflux. When the reaction was over, 94 g. of phenol and 195 g. of ethyl iodide were added. The contents of the flask was then boiled under reflux condenser on a water bath until no longer alkaline to moist litmus. The alcohol and excess ethyl iodide were then distilled off from the water bath. The residue was shaken up with a and extracted with ether. The ethereal extract was washed with a dilute 2% potassium hydroxide solution and finally with water. The ether extract was dried over anhydrous calcium chloride for at least 8 hours. The ether was then distilled off and the residue distilled with an air condenser. The portion boiling over between 167 to 169°C. at atmospheric pressure was 97 g. or 80% of the theoretical.

(2) Phosphorus pentoxide, P_2O_5, was used in its usual manner in an attempt to condense malonic diethyl ester and phenetole.

Materials used:

Malonic diethyl ester.....20 g.

Phenetole.....15 g.

Phosphorus pentoxide.....30 g.

To 20 g. of malonic diethyl ester in a 125 c.c. Claisen side-arm distilling flask were added 15 g. of phenetole and 30 g. of phosphorus pentoxide. The flask was stoppered as tight as possible. Then a series of very interesting color changes in the mixture took place as follows: (1) yellow, (2) orange, (3) orange red, (4) brown, (5) dark brown, and finally (6) to a beautiful purple. All of this occured during an hour. The flask was allowed to stand over-night and then the contents were distilled under a diminished pressure (10 mm.). The distillation products all came over below 110°C., indicating that we had reclaimed our original products in a 90% yield. Ethyl phenyl malonic diethyl ester, the desired product, boils at 151°C., at 10 mm. pressure.

(3) Zinc chloride, $ZnCl_2$, was used in an exceptional manner in an attempt to condense malonic diethyl ester and phenetole.

Materials used:

Malonic diethyl ester.....20 g.

Phenetole.....15 g.

Zinc chloride (anhydrous).....30 g.

To a 200 c.c. pressure flask were added 20 g. malonic diethyl ester, 15 g. of phenetole, and 30 g. of anhydrous zinc chloride. The flask was then clamped and heated in an oil bath for 4 hours at a temperature of about 170°C. The contents of the flask were first extracted with ether and then enough water added to decompose the zinc chloride remaining. The aqueous solution was ex-

tracted with ether and all the ether extracts were combined. The ether extracts were washed with 0.1 M. sodium carbonate solution until neutral and finally with water. The ether solution was dried over anhydrous calcium chloride for at least 8 hours. The ether was distilled off and the residue was distilled at a reduced pressure. In two of the attempts a fraction boiling from 150 to 177°C. was collected. It amounted to 3 g. or a 10% yield. The product might be ethyl phenyl malonic diethyl ester.

VIII. The Condensation of Ethyl Bromomalonic Diethyl Ester and Iodobenzene

It was assumed that the reaction would proceed in accordance with the following reaction.

$$\underset{\text{Iodo-benzene}}{C_6H_5I} + \underset{\text{Ethyl bromomalonic diethyl ester}}{(Br)(C_2H_5)C(CO_2C_2H_5)_2} \xrightarrow{2Na} \underset{\text{Ethyl phenylmalonic diethyl ester}}{(C_6H_5)(C_2H_5)C(CO_2C_2H_5)_2}$$

Diphenyl was obtained as a product in the reaction and indicated that the Wurtz reaction alone occurred:

$$\underset{\text{Iodo-benzene}}{C_6H_5I} + 2Na + C_6H_5I \longrightarrow \underset{\text{Diphenyl}}{C_6H_5C_6H_5} + 2NaI$$

Procedure

(1.) Ethylbromomalonic diethyl ester, $(C_2H_5)(Br)C(CO_2C_2H_5)_2$, was prepared exactly as on page 38. The usual method is to brominate without a solvent[30] in the sunlight, but the method of Palmer[28] is more efficient.

Materials used:

Ethyl malonic diethyl ester..... 63 g.

Carbon tetrachloride.....100 c.c.

Bromine (anhydrous)..... 60 g.

A yield of 55 g., equivalent to 70% of theoretical was obtained boiling between 128 to 130°C., at 17 mm.

This method of bromination of the ethyl malonic diethyl ester is original in its application.

(2) Sodium amalgam, 4% Na, was used in the usual way in an attempt to condense iodobenzene and ethyl bromomalonic diethyl ester.

Materials used:

Ethyl bromo-malonic diethyl ester..... 55 g.

Iodobenzene..... 43 g.

Sodium amalgam (4%).....375 g.

To a 500 c.c. Pyrex flask were added 375 g. of sodium amalgam (15 g. of sodium), 43 g. of iodobenzene and 55 g. of ethyl bromo-malonic diethyl ester. The mixture was placed under reflux and heated for three days on a steam bath. 50 g. of absolute ethyl alcohol were added to the mixture and then cold dilute (10%) sulfuric acid was added until slightly acid. Water was added and the mixture extracted repeatedly with ether. The ether extracts were combined and dried over anhydrous calcium chloride. The ether was distilled and the residue distilled at a reduced pressure (25 mm.). The fractions collected did not go above 130°C. and the fraction from 100 to 130°C. crystallized on cooling. The melting point of the crystals identified them as diphenyl.

Ethyl phenyl malonic diethyl ester boils at 154°C., at 11 mm. No product was obtained at that temperature.

CONCLUSIONS

The present investigation made possible the following improvements in the war-time synthesis of M. Rising and J. Stieglitz:[6] (1)Ethyl phenylmalonic diethyl ester is prepared in better yield and better quality by use of absolute ether as a refluxing agent. (2) "Luminal" is conveniently prepared in a pressure flask with either sodium methylate or sodium ethylate as a condensing agent. (3) Dimethyl oxalate is prepared in much larger yields with less trouble with sulfuric acid as a condensing agent.

It was found that "Luminal" could be prepared by means of the ethyl ester. The procedure was, in general, according to the directions of Rising and Stieglitz.[6] The modifications were used to good advantage in this synthesis.

Three new observations were made as a result of the synthesis of "Luminal" according to Cretcher and Nelson[10] and they are as follows: (1) Phenyl malonic diethyl ester, for the first time to be known, crystallized as long needles with a melting point of 18 to 19°C. (2) Phenyl malonic ethyl ester monoamide, formed from the pure phenyl malonic diethyl ester, has a melting point of 124 to 125°C. This does not agree with the observations of Wislicenus who used an impure phenyl malonic diethyl ester to prepare the amide. (3) Phenyl malonic diamide was obtained for the first time from the pure phenyl malonic diethyl ester and had a melting point of 228 to 230°C. Wislicenus stated that the diamide sublimed and that he did not have enough for analysis. The diamide was obtained in good yield with sufficient to make several analyses.

The syntheses of isoamyl phenyl malonic diethyl ester and 5,5-Isoamyl phenyl barbituric acid represent but a beginning in the possible syntheses of barbituric acids substituted with alkyl and aryl groups in the 5-position. The two compounds are new contributions to the field of organic chemistry. And 5,5-Isoamyl phenyl barbituric acid may be of value as a hypnotic acid sedative due to its similar structure to "Luminal".

There was evidence of the condensation of bromomalonic diethyl ester and benzene with anhydrous aluminum chloride as the condensing agent. However, the yield was so small that no positive proof was looked for. The condensation with zinc dust as the condensing agent yielded products other than desired.

The attempt to condense phenetole and malonic diethyl ester in good yield ended in failure, although no positive proof was obtained that anhydrous zinc chloride effected condensation in a pressure flask.

The preparation of ethyl bromomalonic diethyl ester was a new application of Palmer's method. The product boiled at the temperature stated by Ruhemann[30a] and not that claimed by Bischoff.[30b] The attempt to condense iodobenzene and ethyl bromomalonic diethyl ester ended in failure.

In conclusion, it may be safely said that no method, at the present time, is known for the introduction of the phenyl radical into the malonic ester in good yield. In fact, no proof has been put forward that it has been effected.

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